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New Finding in the Treatment of Neovascular AMD

Polymorphic variability in the VEGFR-2 gene influences responsiveness to treatment with anti-VEGF agents.

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Age-related macular degeneration (AMD) is a sight-impairing condition that affects as many as 15 million Americans.¹ There are several risk factors for the disease, including age, family history, and genetics. Loss of visual acuity occurs either as a consequence of atrophy or neovascularization within the macula.

Drugs that inhibit VEGF are used to maintain visual acuity or prevent further loss of visual acuity in eyes that exhibit signs of neovascular AMD (ie, abnormal blood vessel growth). Unfortunately, treatment response is not uniform. Some patients respond rapidly and require only a few doses of the drug for maintenance of the therapeutic response; others respond poorly and require many doses of treatment over the long term.

We conducted a study to test whether genetic variability could be a cause of the variable treatment response. This article provides a brief description of the study as well as our general findings.

STUDY SPECIFICS

Participants with at least one eye diagnosed with neovascular AMD and being treated with an anti-VEGF regimen were enrolled. Information on visual acuity at baseline, the type of neovascular AMD, and the treatment response over time was extracted in a systematic manner. Participants were classified as responders to treatment, part responders, or nonresponders. If both eyes were affected, this classification was made for each eye individually. Blood samples donated by study participants were subjected to DNA extraction and candidate single-nucleotide polymorphism (SNP) analysis.

A total of 11 genetic loci were chosen for genotyping, and SNPs were selected from within these loci to tag common haplotypes (> 5% frequency within the HapMap CEU population). Clinical characteristics of cases and controls were then compared using the z-test for large independent samples and the χ^2 test. Association analyses were performed using PLINK.² Initially a χ^2 test for trend (1 df) was used. Logistic regression analysis was then performed on each SNP with terms for potential confounders (covariates included) included in the model. The level of statistical significance was set at 5%.

GENERAL FINDINGS

Of the 467 participants enrolled, 43 were excluded from the analysis (age < 55, not treated with anti-VEGF, no exudative AMD, or genetic analysis not performed). Of the remaining 424 study participants, 275 (65%) were classified as macula fluid-free any time and 172 (40%) as macula fluid-free within 3 months.

In the unadjusted analysis, we observed statistically significant associations between several SNPs in the VEGFR-2 gene. We selected the SNP rs17085262 with the lowest *P* value (.007) as the explanatory variable of interest. When the dependent variable was macula fluid-free at any time, the regression model confirmed significant association with responder status in a dose-dependent manner with an odds ratio of 1.38 (CI 0.881, 2.176) for a single copy and 3.22 (1.067, 9.730) with both copies of the minor allele. We then examined time to fluid disappearance by genotype, which showed a progressive increase in response to treatment with a number of copies of the minor allele for the SNP of interest. However, final visual acuity did not differ significantly between the groups.

DISCUSSION

Other groups have suggested that variation in the VEGFA gene itself and in the VEGFR-2 gene can influence functional treatment responses^{3,4}; however, the CATT and IVAN trials, which examined the pharmacogenetics of treatment responsiveness to anti-VEGF therapies, failed to find convincing evidence of modulation of functional outcomes by genetic factors.^{5,6} The CATT trial (and many of the other studies) used visual acuity as the outcome parameter.

We, on the other hand, categorized our outcomes based on morphology as retinal function and obtained the data on visual acuity changes. We chose to use morphological improvement as the main outcome because visual function is influenced not just by amelioration of the anatomical abnormalities, but also by the delivery of a most optimal regimen of treatment. Therefore our data, while suggesting that variation in the VEGFR-2 gene, which encodes the cognate receptor for the VEGFA protein, can influence morphological responsiveness to VEGF therapy in neovascular macular degeneration, are consistent with a lack of functional response.

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